Section II (Remarks)

A. Summary of Amendment to the Claims

Claim 14 has been amended as set forth in the above Complete Listing of the Claims. As amended, the claims are supported by the specification and the original claims and do not add new matter, as defined by 35 U.S.C. § 132. Specifically, amendment of claim 14 is supported in the text of previously pending claim 15 and in the specification at page 4, 4th paragraph and page 5, 1st sentence. New claim 16 is supported in the text of the original claims and throughout the specification, specifically at page 2, line 21 to page 3, line 17.

The amendments do not require a new search, or raise new issues for consideration because they merely address issues already raised by the examiner or define applicants' invention more clearly.

By the present amendment, claims 1, 2, 4, 5, 7, 8, and 15 have been canceled, without prejudice. Claims 3 and 6 were previously canceled.

Thus, upon entry of the amendments, claims 9-14 and 16 will be pending, of which claims 9-13 are withdrawn.

In view of the finality of the June 21, 2011 Office Action and to ensure substantive consideration of this response, a Request for Continued Examination is concurrently submitted herewith, together with payment of the appertaining RCE fees (see *infra*, "Conclusion").

B. Objection to Claim 8

In the Office Action mailed June 21, 2011, claim 8 was objected to. By the present response claim 8 has been cancelled. The objection is therefore moot.

C. Rejection Under 35 U.S.C. §112 - Indefiniteness

In the Office Action mailed June 21, 2011, claims 1, 2, 4, 5, 7 and 8 were rejected under 35 U.S.C. §112, second paragraph as indefinite. By the present response, claims 1, 2, 4, 5, 7 and 8 have been canceled. The rejection is therefore moot and withdrawal of the rejection is respectfully requested.

Claim 14 was rejected under 35 U.S.C. §112, second paragraph as indefinite in recitation of a diagnosis step in the preamble "but there is no resultant step relating the calculated stimulation index to the disease." In accordance with the examiner's suggestion, the subject matter of claim 15 has been incorporated into the method of claim 14. As stated by the examiner, such action is "remedial" of the indefiniteness of the claim. Withdrawal of the rejection is therefore respectfully requested.

D. Rejection Under 35 U.S.C. §112 - Enablement

In the Office Action mailed June 21, 2011, the examiner rejected claims 1, 2, 4, 5, 7, 8 and 14-15 as failing to comply with the enablement requirement. Applicants respectfully traverse the rejection. It is noted that by the present response, claims 1, 2, 4, 5, 7, 8 and 15 have been canceled. Accordingly the rejection is addressed below as applicable to pending claim 14.

The method recited in claim 14 provides a notable advantage over the prior art in that it allows an immediate diagnostic assessment from a single index value. The claimed method provides a specific kind of calculation of the stimulation index, which results in an improved discrimination between patients suffering from Alzheimer's disease and healthy patients. Due to this improved discrimination a diagnostic evaluation is possible from only a single patient's sample without the necessity of control samples or comparative testing. Thus, a new, simple method useful in the diagnosis of Alzheimer's disease is achieved which, advantageously, can be locally carried out, e.g., even in a family physician's practice.

In rejecting the claims, the examiner states that "[t]he scope of the instant claims is broadly drawn to diagnosing not only disease in those who have clinical manifestations of Alzheimer's disease…but in all subjects…" Applicants respectfully disagree. It is recited in the preamble of claim 14 that it is a method "…of determining a mitogenic stimulation index for diagnosing patients suffering from Alzheimer's disease." Additionally part (e) of claim 14 recites, in relevant part "wherein the stimulation index which reaches at least 10, as a maximum 100, is a sign of Alzheimer's disease in a patient sample from a patient suffering from Alzheimer's disease," previously recited in claim 15. By such recitation applicants' claimed method is clearly delimited to patients suffering from Alzheimer's disease.

It is also the examiner's position that the Steiler et al. reference "teaches all of the method steps of the claims, but teaches a significantly **reduced stimulation index** after mitogen treatment..." Applicants respectfully disagree with this statement.

It is respectfully submitted that the stimulation index of the Steiler et al. reference is not directly applicable to the stimulation index in the claimed method, because the two are calculated differently. As recited in claim 14 of the present application, the stimulation index is determined by quantification of the $CD69^+$ lymphocytes, i.e., the number of cells. By contrast, Stieler et al. describes calculation of the stimulation index "as the ratio of CD69-expression" in the sample, i.e. Stieler quantifies the total CD69 molecules in the sample (see page 3970, 1st paragraph). The overall CD69-expression measured by Stieler is a parameter that is different from the number of CD69-positive lymphocytes counted as recited in claim 14 of the present application.

Thus, Stieler teaches a stimulation index distinct from that of the present invention, because the stimulation index of Stieler is based on the measurement of a different parameter, namely the overall CD69 expression in the sample, and therefore Stieler teaches a stimulation index determined in a different way from that of the present invention. Simply stated, the stimulation indices shown in Stieler et al. do not correspond with the stimulation index recited in claim 14 and the two indicies are not directly comparable.

It was a surprising finding by the inventors of the present application that a reproducible stimulation index capable of discriminating between a sample of a patient suffering from Alzheimer's disease and a healthy subject can be obtained, when the stimulation index is calculated as a relationship of the number of lymphocytes bearing the CD69 surface marker. Such calculation is a recited element of the method of claim 14.

In the Declaration of Dr. Arendt provided with the response mailed November 15, 2009, the stimulation index on page 3 of the Declaration corresponds to the index recited in claim 14. The formula in the Declaration shows the quantification of the lymphocytes within the cell population bearing the CD69 surface marker before mitogenic stimulation according to step (b) as the sub-quotient of the number of CD69 surface marker bearing lymphocytes (= n[CD69+] non-stim.) and the total number of lymphocytes in the sample (=n[CD69+] non-stim. + n[CD69-] non-stim.). Corresponding thereto the quantification of lymphocytes according to step (d) after stimulation is obtained as the sub-quotient of the number of CD69 surface marker bearing lymphocytes (=

n[CD69+] PHA-stim.) and the total number of lymphocytes in the stimulated sample (=n[CD69+] PHA-stim. + n[CD69-] PHA-stim.). Such determined sub-quotients represent the quantity of $CD69^+$ lymphocytes within the non-stimulated cell population of step (b) and the stimulated cell population of step (d), respectively, as recited in steps (b) and (d).

Finally, the Declaration shows the stimulation index (SI) as the quotient of the number obtained from step (d) (*i.e.* stimulated sample "PHA-stim.") and the number obtained from step (b) (*i.e.* non-stimulated sample "non-stim."). Thus, the stimulation index shown in the Declaration corresponds with the calculation recited in step (e) of claim 14.

The examiner further states at page 5 of the Final Office Action that the Declaration of Dr. Arendt does not support the scope of claims drawn to any stimulation index above 10 being indicative of Alzheimer's disease because in the Declaration "4 of the control patients had a stimulation index of greater than 10..." However, it is noted that MMSE scores used for classifying the samples into patients and controls do not represent a definitive diagnosis of Alzheimer's disease. Such a definitive diagnosis is only possible post-mortem by autopsy verification. Thus, for example, these 4 control patients could have been in an early stage of the disease without showing the clinical manifestations determined by MMSE.

Claim 14 recites "*a method of determining a mitogenic stimulation index for diagnosing patients suffering from Alzheimer's disease*", i.e., a method which is useful in the diagnosis of Alzheimer's disease. Step (e) of claim 14 recites "*the stimulation index which reaches at least 10, as a maximum 100, is a sign of Alzheimer's disease in a patient sample from a patient suffering from Alzheimer's disease*", i.e. a stimulation index of at least 10 indicates Alzheimer's disease. The Declaration of Dr. Arendt shows that reproducible results can be obtained by the claimed method. The Declaration supports the full scope of the method of claim 14.

Finally, the examiner alleged that the experiments disclosed in Dr. Arendt's declaration are correlated to MMSE scores of below 27, while the claims are not so limited to such manifestations of the disease. An MMSE score below 27 indicates cognitive impairment (see page 3 of the Declaration) and claim 14 is limited to "patients suffering from Alzheimer's disease", i.e., persons having a score of below 27. There is therefore correlation between the patients specified in the method of claim 14 and the subjects used to generate the empirical evidence presented in the Declaration.

On the basis of the specification, the working examples provided, and the corroborative evidence of Dr. Arendt's Declaration, applicants respectfully submit that one skilled in the art would have been enabled to make and use the claimed invention without undue experimentation based on the disclosures in the application. Claim 14 therefore complies with the enablement requirement of 35 U.S.C. §112 and withdrawal of the rejection is respectfully requested.

CONCLUSION

Based on the foregoing, applicants' pending claims 14 and 16 are patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing and to responsively issue a Notice of Allowance.

The time for responding to the June 21, 2011 Office Action without extension was set at three months, or September 21, 2011. Applicants hereby request a two month extension of time for response under 37 CFR § 1.136 to extend the deadline to November 21, 2011. Payment of the extension fee of $280.00 specified in 37 C.F.R. § 1.17(a)(2) and the RCE fee of $465.00 specified in 37 C.F.R. § 1.17(e), as applicable to small entity, is being made by on-line credit card authorization at the time of EFS submission of this Response. Should any additional fees be required or an overpayment of fees made, please debit or credit our Deposit Account No. 08-3284, as necessary.

If any issues require further resolution, the examiner is requested to contact the undersigned attorneys at (919) 419-9350 to discuss same.

Respectfully submitted,

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